INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/001236

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:

   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-27, 29-48	as originally filed
28	received on 10.01.2006 with letter of 09.01.2006

Claims, Numbers

1-32	received on 10.01.2006 with letter of 09.01.2006

Drawings, Sheets

1/6-6/6	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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PCT/GB2005/001236

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 29

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 29

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/001236

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8-15,18,19
	No:	Claims	1-7,16,17,20-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-28,30-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/GB2005/001236

Re Item III.

Claim 29 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

Reference is made to the following documents:

D3 : WO 02/10120 A (PHOTOCURE ASA; GOLDING, LOUISE; KLAVENESS, JO; NILSEN, NILS, OLAV; BRA) 7 February 2002 (2002-02-07)
D4 : US 6 034 267 A (GIERSKCKY ET AL) 7 March 2000 (2000-03-07)

In the light of, D3 (page 11, lines 24-31; claims 1-25) as well as D4 (col. 4, lines 40-47; claims 1-16) claims 1-7,16,17 and 20-32 cannot be considered as being novel (Art. 33(2) PCT).

In addition to that, in the light of D3 and D4 the present claims 1-32 cannot be considered as being inventive (Art. 33(3) PCT) as the object of the present application, namely to provide ALA compounds with enhanced stability has already been described or at least suggested by the cited documents.

For the assessment of the present claim 29 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII.

The word "about" used in connection with numerical ranges obscures the scope of protection sought (Art. 6 PCT).
The terms "alkyl group" and "aryl group" are too broad in scope and not fully supported by the present specification. The Applicant's attention is drawn to the fact that expressions like "e.g." have no limiting effect on the scope of the claim, that is to say, the feature following such an expression is to be regarded as entirely optional.

application of cream formulations containing hydrochloride, tosylate and mesylate salts of benzyl 5-amino-4-oxopentanoate, bars indicate standard deviation;

Figure 3 shows skin fluorescence following topical application of cream formulations containing hydrochloride and methanesulfonate salts of methyl 5-amino-4-oxopentanoate, bars indicate standard deviation;

Figure 4 shows skin fluorescence following topical application of cream formulations containing hydrochloride, methanesulfonate and toluenesulfonate salts of hexyl 5-amino-4-oxopentanoate, bars indicate standard deviation;

Figure 5 shows skin fluorescence following topical application of cream formulations containing hydrochloride and hydrobromide salts of 5-amino-4-oxopentanoic acid, bars indicate standard deviation;

Figure 6 shows skin fluorescence following topical application of cream formulations containing hydrochloride, hydrobromide and nitrate salts of benzyl 5-amino-4-oxopentanoic acid, bars indicate standard deviation;

Figure 7 shows skin fluorescence following topical application of cream formulations containing hydrochloride, sulphate and phosphate salts of benzyl 5-amino-4-oxopentanoic acid, bars indicate standard deviation;

Figure 8 shows the hygroscopicity of hydrochloride, methanesulfonate and toluenesulfonate salts of methyl 5-amino-4-oxopentanoic acid;

Figure 9 shows the hygroscopicity of hydrochloride and toluenesulfonate salts of 5-amino-4-oxopentanoic acid; and

Figure 10 shows the hygroscopicity of hydrochloride, methanesulfonate and toluenesulfonate salts of hexyl 5-amino-4-oxopentanoic acid.

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Claims:

1. An acid addition salt of a 5-aminolevulinic acid (5-ALA) derivative (e.g. a 5-ALA ester) with an acid which has a pKa of about 5 or less, preferably about 3 or less, wherein said acid is a sulfonic acid, a sulfonic acid derivative, sulfuric acid, nitric acid or phosphoric acid.

2. An acid addition salt as claimed in claim 1 which is derived from a compound of formula X:

$R^2{}_2N\text{-}CH_2COCH_2\text{-}CH_2CO\text{-}OR^1$ (X)

(wherein R^1 represents an optionally substituted straight-chained, branched or cyclic alkyl group which may optionally be interrupted by one or more -O-, $-NR^3-$, -S- or $-PR^3-$ groups;
R^2 each independently represents a hydrogen atom or an optionally substituted straight-chained, branched or cyclic alkyl group which may optionally be interrupted by one or more -O-, $-NR^3-$, -S- or $-PR^3-$ groups; and
R^3 is a hydrogen atom or a C_{1-6} alkyl group).

3. An acid addition salt as claimed in claim 2, wherein in formula X, R^1 either represents an unsubstituted alkyl group (e.g. C_{1-6} alkyl) or an alkyl group (e.g. C_{1-2} alkyl) substituted by an aryl group (e.g. phenyl) and/or each R^2 represents a hydrogen atom.

4. An acid addition salt as claimed in claim 2 or claim 3, wherein R^1 is a benzyl or substituted benzyl group.

5. An acid addition salt as claimed in claim 2, wherein said compound of formula X is 5-ALA methyl ester, 5-ALA hexyl ester, 5-ALA benzyl ester, 5-ALA 2-

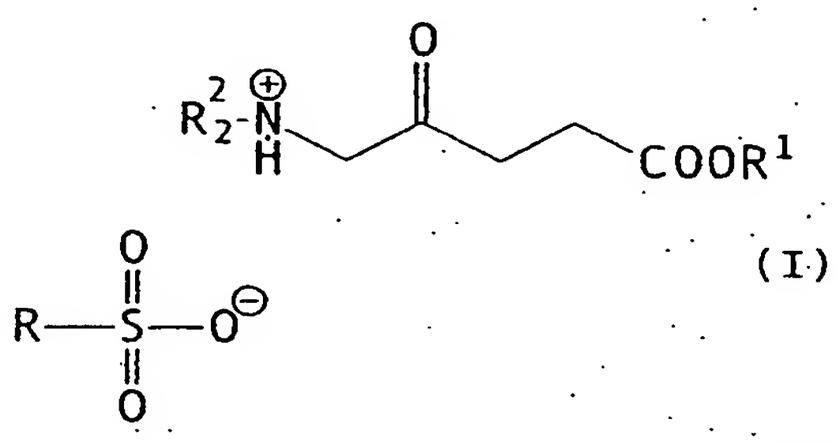
methylpentyl ester, 5-ALA 4-methylpentyl ester, 5-ALA 2-(2-ethoxyethoxy)ethyl ester, 5-ALA 4-methylbenzyl ester or 5-ALA 4-isopropylbenzyl ester.

6. An acid addition salt as claimed in claim 2, wherein said compound of formula X is 5-ALA methyl ester, 5-ALA hexyl ester or 5-ALA benzyl ester.

7. An acid addition salt as claimed in any one of claims 1 to 6, wherein said acid is an organic acid.

8. An acid addition salt as claimed in claim 7, wherein said acid is a sulfonic acid or a sulfonic acid derivative.

9. An acid addition salt as claimed in claim 1 of formula I:



(I)

(wherein
R is a hydrogen atom or an optionally substituted alkyl (e.g. a C_{1-20} alkyl group) or aryl group (e.g. an aryl group of up to 20 carbon atoms), preferably an optionally substituted alkyl or aryl group;
R^1 represents an optionally substituted straight-chained, branched or cyclic alkyl group which may optionally be interrupted by one or more -O-, $-NR^3-$, -S- or $-PR^3-$ groups;
R^2 each independently represents a hydrogen atom or an optionally substituted straight-chained, branched or cyclic alkyl group which may optionally be interrupted by one or more -O-, $-NR^3-$, -S- or $-PR^3-$ groups; and

R^3 is a hydrogen atom or a C_{1-6} alkyl group).

10. An acid addition salt as claimed in claim 9, wherein R is optionally substituted phenyl or methyl.

11. An acid addition salt as claimed in claim 9 or claim 10, wherein in formula I, R^1 either represents an unsubstituted alkyl group (e.g. C_{1-6} alkyl) or an alkyl group (e.g. C_{1-2} alkyl) substituted by an aryl group (e.g. phenyl) and/or each R^2 represents a hydrogen atom.

12. An acid addition salt as claimed in any one of claims 9 to 11, wherein R^1 is a benzyl or substituted benzyl group.

13. An acid addition salt as claimed in claim 9 which is a sulfonic acid addition salt of 5-ALA methyl ester, 5-ALA hexyl ester, 5-ALA benzyl ester, 5-ALA 2-methylpentyl ester, 5-ALA 4-methylpentyl ester, 5-ALA 2-(2-ethoxyethoxy)ethyl ester, 5-ALA 4-methylbenzyl ester or 5-ALA 4-isopropylbenzyl ester.

14. An acid addition salt as claimed in claim 9 which is a sulfonic acid addition salt of 5-ALA methyl ester, 5-ALA hexyl ester or 5-ALA benzyl ester.

15. An acid addition salt as claimed in claim 13 or claim 14, wherein said acid is napthalene-1,5-disulfonic acid, ethane-1,2-disulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, dodecylsulfonic acid, napthalene-2-sulfonic acid, benzenesulfonic acid, 2-hydroxy-ethanesulfonic acid, ethanesulfonic acid, or (+)-camphor-10-sulfonic acid.

16. An acid addition salt as claimed in any one of claims 1 to 6, wherein said acid is an inorganic acid.

17. An acid addition salt as claimed in claim 17, wherein said acid is sulfuric acid, nitric acid or phosphoric acid, preferably nitric acid.

18. An acid addition salt as claimed in any one of claims 1 to 6, wherein said acid is a sulfonic acid, a sulfonic acid derivative or nitric acid.

19. An acid addition salt as claimed in any preceding claim, wherein said acid is pharmaceutically acceptable.

20. A process for preparing an acid addition salt as claimed in any one of claims 1 to 19, said process comprising reacting a 5-aminolevulinic acid derivative (e.g. an ALA ester) with an acid as defined in claim 1.

21. A process for the preparation of an acid addition salt as claimed in any one of claims 1 to 19, said process comprising the reaction of 5-aminolevulinic acid, or an esterifiable derivative thereof, with an alkanol or an ester-forming derivative thereof (e.g. with an alkanol) in the presence of an acid as defined in claim 1.

22. A process for the preparation of an acid addition salt as claimed in any one of claims 1 to 19 (e.g. a compound of formula I), said process comprising:

(i) contacting a solution comprising a hydrochloride salt of an ALA derivative (e.g. a compound of the formula $Cl^- R^2{}_2N^+H\text{-}CH_2COCH_2CH_2CO_2R^1$ wherein R^1 and R^2 are as defined in claim 2) with a basic anion exchange resin;

(ii) optionally removing said resin; and

(iii) mixing the resulting solution with a solution comprising an acid as defined in claim 1, preferably a sulfonic acid or a sulfonic acid derivative.

23. A process for the preparation of an acid addition salt as claimed in any one of claims 1 to 19 (e.g. a compound of formula I), said process comprising:

(i) reacting a hydrochloride salt of an ALA derivative (e.g. a compound of the formula $Cl^- R^2_2N^+H\text{-}CH_2COCH_2CH_2CO_2R^1$ wherein R^1 and R^2 are as defined in claim 2) with a silver salt of an acid as defined in claim 1, preferably a sulfonic acid or a sulfonic acid derivative, in a solvent in which AgCl is substantially insoluble; and

(ii) optionally separating AgCl from the resulting salt.

24. An acid addition salt obtainable by contacting (e.g. reacting) a 5-ALA derivative (e.g. a 5-ALA ester) with an acid as defined in claim 1.

25. A acid addition salt obtainable by a process as claimed in any one of claims 20 to 23.

26. A pharmaceutical composition comprising an acid addition salt as claimed in any one of claims 1 to 19, 24 or 25, together with at least one pharmaceutical carrier or excipient.

27. An acid addition salt or composition as claimed in any one of claims 1 to 19, 24, 25 or 26 for use as a medicament, e.g. for use in photodynamic therapy.

28. Use of an acid addition salt as claimed in any one of claims 1 to 19, 24, 25 or 26 for the preparation of a therapeutic agent for use in photochemotherapy, preferably for the treatment of disorders or abnormalities of external or internal surfaces of the body which are responsive to photochemotherapy.

29. A method of photochemotherapeutic treatment of disorders or abnormalities of external or internal surfaces of the body, said method comprising administering to the affected surfaces, an acid addition salt or composition as claimed in any one of claims 1 to 19, 24, 25 or 26, and exposing said surfaces to light (e.g. white light), preferably to light in the wavelength region 300-800 nm (e.g. blue light in the wavelength region 380-440 nm).

30. A product comprising an acid addition salt as claimed in any one of claims 1 to 19, 24, 25 or 26, together with at least one surface-penetration assisting agent, and optionally one or more chelating agents as a combined preparation for simultaneous, separate or sequential use in treating disorders or abnormalities of external or internal surfaces of the body which are responsive to photochemotherapy.

31. A kit for use in photochemotherapy of disorders or abnormalities of external or internal surfaces of the body comprising:

a) a first container containing an acid addition salt as claimed in any one of claims 1 to 19, 24, 25 or 26,

b) a second container containing at least one surface penetration assisting agent; and optionally

c) one or more chelating agents contained either within said first container or in a third container.

32. A method of *in vitro* diagnosis of abnormalities or disorders by assaying a sample of body fluid or tissue of a patient, said method comprising at least the following steps:

i) admixing said body fluid or tissue with an acid addition salt as claimed in any one of claims

1 to 19, 24, 25 or 26,

ii) exposing said mixture to light,

iii) ascertaining the level of fluorescence, and

iv) comparing the level of fluorescence to control levels.